General

Guideline Title

Combined hormonal contraception and the risk of venous thromboembolism: a guideline.

Bibliographic Source(s)

Practice Committee of the American Society for Reproductive Medicine. Combined hormonal contraception and the risk of venous thromboembolism: a guideline. Fertil Steril. 2017 Jan;107(1):43-51. [91 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the level of the evidence (Level I-III) and strength of the recommendations (Grade A-C) are given at the end of the "Major Recommendations" field.

Does the Dose of Estrogen Affect Venous Thromboembolism (VTE) Rates?

Summary Statement

There are no randomized trials large enough to compare thrombosis risk in patients on oral contraceptives containing different doses of ethinyl estradiol (EE). Only level II-2 studies exist, including large cohort and case-control studies. It is difficult to compare the effect of the EE dose since preparations differ with respect to the progestin component. In addition, observational studies are limited by a number of unmeasured confounders and bias. The following may be concluded from the literature:

- While no longer available in the United States, high-dose combined oral contraception (COC) (>50 µg) is associated with higher risks of VTE than lower-dose formulations. (Grade B)
- There is fair evidence that combined oral contraception with 50 µg EE has a higher risk of thrombosis compared with sub-50 µg EE formulations. (Grade B). However, data are conflicting and difficult to interpret due to the variable progestin component of the pills studied.
- There is fair evidence that COCs containing EE doses lower than 35 µg have similar VTE risk to 35 µg formulations. (Grade B)

Does Type of Progestin Contribute to VTE Risk?

Summary Statement

There are no randomized trials large enough to compare the risk of VTE in patients on different types of oral contraceptives. Only level II-2 studies exist, including large cohort and case-control studies. It is difficult to compare the effect of the progestin component alone, as some studies include preparations with different doses of EE. In addition, observational studies are limited by a number of confounders and bias (including differences in users and non-users of COCs, duration of combined oral contraception use, and misclassification of VTE due to differences in diagnostic criteria used).

Because of the lack of high-quality level I studies comparing progestins, it is possible that methodological problems in the present studies are responsible for the small increased risk in VTE events, and that there is actually no increased risk with third- or fourth-generation progestins, such as desogestrel or drospirenone. If there is indeed an increased relative risk (RR), the absolute risk increase is extremely small. Therefore, in the appropriately selected patient, the choice of COC method does not need to be made based on the type of progestin. If a woman has estrogen-related COC risk for VTE, then no route of administration or dose of estrogen has been found to be safer. All estrogen-containing hormonal methods are contraindicated in that setting.

- There is fair evidence that all available combined hormonal contraceptive (CHC) preparations increase the risk of VTE over the non-pregnant state.
- There is fair evidence that women using preparations of COC with drospirenone or third-generation progestins have a slightly higher risk of VTE compared with those using norethindrone or levonorgestrel. (Grade B). These results may in part be related to characteristics of the populations using these preparations.

Does Route of Administration of CHC Contribute to VTE Risk?

Summary Statement

All of the studies addressing this question were level II-III.

There is insufficient evidence that the contraceptive patch or contraceptive vaginal ring has a different risk of VTE compared with COCs. (Grade C)

Are Smoking, Obesity, or Inherited Thrombophilias Risk Factors for VTE in CHC Users?

Summary Statement

Several level II and III studies have identified risk factors associated with VTE; however, determining to what degree a specific risk factor increases the risk of VTE is difficult as these studies are heterogeneous and are often confounded by biases.

- There is fair evidence that tobacco use, age (>35 years), obesity, and the presence of hereditary thrombophilias (including factor V Leiden mutation, prothrombin G20210A mutation and protein C, protein S, or antithrombin deficiency) increase the risk of thrombotic events in the setting of CHC use. (Grade B)

Recommendation

In the patient in whom combined hormonal contraception is appropriate, it is reasonable to use any currently available preparation.

Definitions

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Strength of Recommendations

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Unintended pregnancy
- Menstrual disorders

Guideline Category

Prevention

Risk Assessment

Clinical Specialty

Family Practice

Internal Medicine

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the association between combined hormonal contraception (CHC) and the risk of venous thromboembolism (VTE)

Target Population

Women using combined hormonal contraception (CHC)

Interventions and Practices Considered

1. Dose of estrogen used
2. Type of progestin used (drospirenone or third-generation progestin versus norethindrone or levonorgestrel)

3. Route of administration of combined hormonal contraception (CHC) (e.g., contraceptive patch or contraceptive vaginal ring versus oral pill) (*insufficient evidence to make a recommendation*)
4. Assessment of risk factors for venous thromboembolism (e.g., smoking, obesity, inherited thrombophilias)

Major Outcomes Considered

- Relative and absolute risk of venous thromboembolism (VTE)
- VTE rates

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search

A systematic literature search of relevant articles was performed in the electronic database MEDLINE through PubMed (February and June 2015), with a filter for human subject research.

A combination of the medical subject headings or text words/keywords were used: birth control; contraception; combined hormonal contraception; combined oral contraceptive; combined oral contraceptives; contraceptives, oral; contraceptives, oral/administration and dosage; contraceptives, oral, combined; contraceptives, oral, combined/administration and dosage; hormonal contraception; oral contraceptive; oral contraceptives; desogestrel; drospirenone; estradiol; estrogen; oestrogen; ethynodiol diacetate; etynodiol diacetate; levonorgestrel; nomegestrol; norethisterone; norethisteron; norethindrone; norethindron; norethynodrel; norgestimat; norgestimate; norgestrel; AND ethinyl estradiol; ethinyl estradiol; ethinylestradiol; mestranol; progesterone; progestin; progestins; progestogen; progestogens; AND cerebral vein thrombosis; clot; deep vein thrombosis; deep venous thrombosis; DVT; embolism; hepatic thrombosis; mesenteric venous thrombosis; pulmonary emboli*; pulmonary embolism; thrombosis; thrombus; thromboembolism; thrombophlebitis; vein embolism; vein thrombosis; venous embolism; venous thromboembolism; venous thrombosis; venous thrombosis; venous thrombotic; first generation, second generation, third generation, fourth generation; AND obese; obesity; body weight; body weight; body mass index; BMI; PCOS; polycystic ovaries; polycystic ovary; polycystic ovary syndrome; polycystic ovarian syndrome; smoking; age; risk, risks, risk factor, risk factors.

Inclusion/Exclusion Criteria

Include	**Exclude**
Level 1, 2-1, 2-2 studies; 2-3	Case reports, reviews, opinions, off topic
Human studies	Animal studies
English	Non-English
Limit to products available in the USA only	Gestodene and cyproterone acetate-containing product
Combined contraception only	Progestin-only preparations
Venous events only	Stroke, coronary/heart attack, arterial
Oral, vaginal, transdermal OR patch	Barrier, injectable
Co-factors: include smoking; obesity; polycystic ovary syndrome (PCOS); inherited thrombophilias	In vitro fertilization (IVF)

Include	Exclude
Reproductive-age women	Peri- and postmenopausal women; menopausal hormone therapy
	Hormone-replacement therapy (HRT) patients
	Emergency contraception
	Surrogate markers

An independent panel of experts reviewed the full articles of all citations that possibly matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and solved by consensus or arbitration after consultation with an independent reviewer/epidemiologist. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a treatment correlated with an outcome measure (VTE); meta-analyses; and relevant articles from bibliographies of identified articles.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

Number of Source Documents

The electronic search and examination of reference lists from primary and review articles yielded 1,254 studies, of which 86 studies were included.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The quality of the evidence for each reference in the bibliography (see the original guideline document) was evaluated using the grading system found in the "Rating Scheme for the Strength of the Evidence" field.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Questions

The literature was reviewed to answer the following questions:

1. Does type of progestin affect venous thromboembolism (VTE) rates?
2. Is route of OCP (oral contraception pills) administration (patch, oral, vaginal) a co-factor for VTE?
3. Does the dose of estrogen (<35 mcg vs >35 mcg) in OCPs affect VTE rates?
4. Are smoking, obesity, PCOS, or inherited thrombophilias co-factors for VTE in women taking OCPs?

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document was reviewed by American Society for Reproductive Medicine members, and their input was considered in the preparation of the final document. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each summary statement that supports the recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The benefits of any currently available combined oral contraceptive to prevent pregnancy outweigh the risks for most women. When selecting a particular combined hormonal contraceptive preparation, any potential risk of venous thromboembolism should be balanced with the potential

benefits associated with each preparation.

Potential Harms

Combined oral contraceptives increase the risk of venous thromboembolism (VTE). Women taking preparations containing drospirenone and third-generation progestins appear to be at slightly increased risk of VTE compared with those taking first- and second-generation preparations.

Contraindications

Contraindications

If a woman has estrogen-related combined oral contraception (COC) risk for venous thromboembolism (VTE), then no route of administration or dose of estrogen has been found to be safer. All estrogen-containing hormonal methods are contraindicated in that setting.

Qualifying Statements

Qualifying Statements

- This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations.
- There are no large, prospective randomized studies comparing the risk of venous thromboembolism (VTE) among various doses of estrogen, types of progestin, or routes of administration. Only level II-2 studies exist, including large cohort and case-control studies that are limited by a number of methodological issues which may skew results. For example, without randomization, it is difficult to control for different patient populations and prescriber bias. It is also important to recognize that VTE risk is greater in new hormonal contraceptive users during the first year, in older women, and in obese women. Many studies do not adequately account for imbalances in these risk factors between treatment groups. In addition, the diagnosis of venous thrombosis may not always be accurate in studies since cases are not always confirmed by hospital records or radiologic studies. Finally, given that the incidence of VTE is low, large numbers of observations are required to compare cases among various treatment groups.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Practice Committee of the American Society for Reproductive Medicine. Combined hormonal contraception and the risk of venous thromboembolism: a guideline. Fertil Steril. 2017 Jan;107(1):43-51. [91 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Jan

Guideline Developer(s)

American Society for Reproductive Medicine - Nonprofit Organization

Source(s) of Funding

American Society for Reproductive Medicine

Guideline Committee

Practice Committee of the American Society for Reproductive Medicine

Composition of Group That Authored the Guideline

Committee Members: Samantha Pfeifer, MD; Samantha Butts, MD, MSCE; Daniel Dumesic, MD; Gregory Fossum, MD; Clarisa Gracia, MD, MSCE; Andrew La Barbera, PhD; Jennifer Mersereau, MD; Randall Odem, MD; Alan Penzias, MD; Margareta Pisarska, MD; Robert Rebar, MD; Richard Reindollar, MD; Mitchell Rosen, MD; Jay Sandlow, MD; Rebecca Sokol, MD, MPH; Michael Vernon, PhD; Eric Widra, MD

Financial Disclosures/Conflicts of Interest

All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the American Society for Reproductive Medicine Web site .

Availability of Companion Documents

Continuing medical education (CME) credit related to this guideline is available from the American Society for Reproductive Medicine Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on March 27, 2017. The information was verified by the guideline developer on April 17, 2017.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.